REMARKS

Interview request

Applicants respectfully request a telephonic interview after the Examiner has reviewed the instant response and amendment. Applicants request the Examiner call Applicants' representative at (858) 720-5133.

Status of the Claims

Pending claims

Claims 42 to 55 and 93 to 106 are pending.

Claims amended, canceled and added in the instant amendment

Claim 107 is added. Thus, after entry of the instant amendment, claims 42 to 55 and 93 to 107 will be pending.

Outstanding Rejections

Claims 42 to 55 and 93 to 106 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite. Claims 42 to 55 remain rejected, and claims 93 to 104 and 106 are newly rejected, under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. Claims 42 to 55 remain rejected, and claims 93 to 104 and 106 are newly rejected under 35 U.S.C. §112, first paragraph, as allegedly not described in the specification in such a way as to enable one skilled in the art to which it pertains to make and/or use the invention.

Applicants respectfully traverse all outstanding objections to the specification and rejections of the claims.

Support for the claim amendments

The specification sets forth an extensive description of the invention in the new and amended claims filed in this and previous responses. For example, support for claims directed to methods using stringent hybridization wash conditions can be found, inter alia, on page 45, paragraph [0144], of the specification. Support for claims directed

to methods wherein amidase activity comprises catalysis of the hydrolysis of an amine group in N.alpha.-carbonylbenzyloxy-L-alanine-7-amido-4-methylcoumarin (CBZ-L-ala-AMC); N.alpha.-carbonylbenzyloxy-L-arginine-7-amido-4-methylcoumarin (CBZ-L-arg-AMC); or, N.alpha.-carbonylbenzyloxy-D-arginine-7-amido-4-methylcoumarin (CBZ-D-arg-AMC), can be found, e.g., in Example 3, pages 85 to 87.

Specification

Trademarks

The specification has been amended to capitalize trademarked products and processes.

Claim Objections

The specification has been amended to address the objection to claim 100.

Issues under 35 U.S.C. §112, second paragraph

Claims 42 to 55 and 93 to 106 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite.

Applicants respectfully aver that the instant amendment addresses all of the issues raised in paragraphs 5 through 8, pages 3 and 4, of the instant office action.

Issues under 35 U.S.C. §112, first paragraph, written description

Claims 42 to 55 remain rejected, and claims 93 to 104 and 106 are newly rejected, under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement.

Because the size of the genus of nucleic acids used in the claimed methods may be a concern to the Patent Office, merely to expedite prosecution of the instant application, and without prejudice or disclaimer, the instant amendment modifies the genus to encompass sequences having at least 90% sequence identity to a sequence as set

forth in SEQ ID NO:1, wherein the sequence encodes a polypeptide having amidase activity.

Applicants respectfully maintain that the claimed invention is sufficiently described in the specification so that one of ordinary skill in the art would be able to ascertain the scope of the claims with reasonable clarity and recognize that Applicants' were in possession of the claimed invention at the time of filing. As discussed in their last response of February 12, 2004, Applicants respectfully submit that describing a genus of polynucleotides in terms of physico-chemical properties (e.g., a % sequence identity or stringent hybridization to an exemplary nucleic acid or polypeptide) and function (e.g., encoding a polypeptide having amidase activity) satisfies the written description requirement of section 112, first paragraph. Also as previously noted, Applicants respectfully aver that the disclosed amidase species of the claimed invention, SEQ ID NO:1 and SEQ ID NO:2, are sufficient to put one of skill in the art in possession of the attributes and features of all species within the genus of nucleic acids of the invention. In fact, both the Patent Office and the Federal Circuit set forth conditions where a single species is sufficient to put one of skill in the art in possession of the attributes and features of all species within a genus, where the genus is defined in terms of shared physical and structural properties with the single species.

Applicants have referred to the USPTO guidelines concerning compliance with the written description requirement of U.S.C. §112, first paragraph, and noted that Example 14 of the Guidelines states that a description of a genus of polynucleotides in terms of its physico-chemical properties, e.g., a % sequence identity, to a single exemplary species, and a common function satisfies the written description requirement of section 112, first paragraph, for the genus of polynucleotides. Analogously, the genus of claimed nucleic acids and polypeptides are described by structure (the exemplary SEQ ID NO:1 and SEQ ID NO:2), a physico-chemical property (a percent sequence identity to an exemplary sequence or stringent hybridization to an exemplary nucleic acid) and function (having amidase activity). After entry of the instant amendment, species of the

genus of nucleic acids used in the claimed methods must have at least 90% or more sequence identity to a sequence as set forth in SEQ ID NO:1 or SEQ ID NO:2. Because the USPTO guidelines recognize that written description is met for a genus of polypeptides described by structure, a physico-chemical property (e.g., a % sequence identity, stringent hybridization) and a defined function, the claimed genus of polypeptides and nucleic acids also meet the written description requirements of section 112.

Also as noted in their earlier response, the Federal Circuit addressed the written description requirement in the context of DNA-related inventions in Enzo Biochem. Inc. v. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by 'showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . *i.e.*, complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.'" [Emphasis added] Id. at 1324, 63 USPQ2d at 1613. The court in Enzo adopted its standard from the USPTO's Written Description Examination Guidelines. See 296 F.3d at 1324, 63 USPQ2d at 1613. The Guidelines apply to proteins as well as DNAs.

Analogously, the functions of the claimed enzymes are sufficiently correlated to a particular, known structure (the exemplary sequence) and a physical (physico-chemical) property (percent sequence identity or stringent hybridization). Furthermore, the invention has been shown to be complete by disclosure of sufficiently detailed, relevant identifying characteristics in the form of structure (sequence), physical and/or chemical properties (percent sequence identity, binding under stringent hybridization conditions) and function (amidase activity). Accordingly, the species of claimed polypeptides are defined via shared physical and structural properties in terms that convey with reasonable clarity to those skilled in the art that Applicants, as of the filing date and at the time of the invention, were in possession of the claimed invention.

The Patent Office alleges structural features (structural elements) for members of the genus of nucleic acids used in the claimed methods need to be described to adequately describe the genus (see page 5, lines 18 and 19; page 6, lines 10 to 17, of the office action). However, because the instant description has met the requirements set forth by the courts and the USPTO's written description guidelines, inter alia, the invention has been shown to be complete by disclosure of sufficiently detailed, relevant identifying characteristics such as structure, physical and/or chemical properties and function shared by all members of the genus, it is not necessary for the specification to set forth additional "structural features/ elements" as alleged by the Patent Office.

The claimed subject matter need not be described in haec verba to satisfy the description requirement. It is not necessary that the application describe the claim limitations exactly, but only so clearly that one having ordinary skill in the pertinent art would recognize from the disclosure that applicants invented the claimed subject matter. In re Herschler, 591 F.2d 693, 700, 200 USPQ 711,717 (CCPA 1979). See also Purdue Pharma L.P. v. Faulding, Inc., 230 F.3d 1320, 1323, 56 USPQ2d 1481, 1483 (Fed. Cir. 2000) ("In order to satisfy the written description requirement, the disclosure as originally filed does not have to provide in haec verba support for the claimed subject matter at issue.").

The Patent Office remains concerned that the issue of "any function" was not sufficiently addressed in Applicants' last response (see paragraph 12, pages 5 to 6, of the instant office action ("OA"). The Patent Office alleges that the specification does not teach amidase activities other than that of the polypeptide of SEQ ID NO:2 (please note page 5, paragraph 12, lines 10 to 20). It was also noted that amidases belong to a family of enzymes which can have diverse substrates and biological functions. Applicants' previous and current amendments intend to clarify that the claimed methods only encompass methods for making variants of nucleic acids encoding amidases of the invention. Thus, to further address the Office's concerns, the claims are amended to be directed to methods wherein amidase activity comprises catalysis of the hydrolysis of an

amine group in N.alpha.-carbonylbenzyloxy-L-alanine-7-amido-4-methylcoumarin (CBZ-L-ala-AMC); N.alpha.-carbonylbenzyloxy-L-arginine-7-amido-4-methylcoumarin (CBZ-L-arg-AMC); or, N.alpha.-carbonylbenzyloxy-D-arginine-7-amido-4-methylcoumarin (CBZ-D-arg-AMC); or, an activity equivalent to the amidase activity of a polypeptide having a sequence as set forth in SEQ ID NO:2.

Applicants respectfully submit that the specification is sufficient to put one of skill in the art in possession of the attributes and features of all species within the genus of nucleic acids of the invention. Thus, the pending claims meet the written description requirement under 35 U.S.C. §112, first paragraph. In light of the above remarks, Applicants respectfully submit that the (amended) claims are sufficiently described in the specification to overcome the rejection based upon 35 U.S.C. §112, first paragraph.

Issues under 35 U.S.C. §112, first paragraph, enablement

Claims 42 to 55 remain rejected, and claims 93 to 104 and 106 are newly rejected under 35 U.S.C. §112, first paragraph, as allegedly not described in the specification in such a way as to enable one skilled in the art to which it pertains to make and/or use the invention.

The Patent Office states that the specification is enabling for methods using the polynucleotide of SEQ ID NO:1, which encodes a polypeptide having amidase activity, or the polypeptide of SEQ ID NO:2. The Office also notes that creation of variants having the structural limitations recited in the claims is routine in the art (see, e.g., page 9, lines 16 and 17, of the OA).

Applicants respectfully maintain that the specification enabled the skilled artisan at the time of the invention to identify, and make and use, a genus of polypeptides having amidase activity, and the nucleic acids that encode them, to practice the claimed invention – and, in addition to their previous arguments (all incorporated by reference herein), will provide additional evidence and expert declaration to support this argument.

However, Applicants respectfully aver that the Patent Office has not met its initial burden to establish a reasonable basis to question the enablement provided for the claimed invention, and as specifically addressed, below, how the art used to support the Office's enablement rejection is not sufficient to rebut the presumptively enabled specification.

But first, because the size of the genus of nucleic acids used in the claimed methods may be a concern to the Patent Office, merely to expedite prosecution of the instant application and without prejudice or disclaimer, Applicants note that the instant amendment modifies the genus to encompass sequences having at least 90% sequence identity to a sequence as set forth in SEQ ID NO:1, wherein all species of this genus encode a polypeptide having an amidase activity.

The Patent Office also remains concerned that the issue of "any function" was not sufficiently addressed in Applicants' last response (see paragraph 15, lines 18 to 23 of page 8, of the OA). Applicants' previous and current amendments intend to clarify that the claimed methods only encompass methods for making variants of nucleic acids encoding amidases of the invention. Thus, to further address the Office's concerns, the claims are amended to be directed to methods wherein amidase activity comprises catalysis of the hydrolysis of an amine group in N.alpha.-carbonylbenzyloxy-L-alanine-7-amido-4-methylcoumarin (CBZ-L-ala-AMC); N.alpha.-carbonylbenzyloxy-L-arginine-7-amido-4-methylcoumarin (CBZ-L-arg-AMC); or, N.alpha.-carbonylbenzyloxy-D-arginine-7-amido-4-methylcoumarin (CBZ-D-arg-AMC); or, an activity equivalent to the amidase activity of a polypeptide having a sequence as set forth in SEQ ID NO:2.

Applicants respectfully aver that the Patent Office has not met its initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)

(examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. As stated by the court, "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." In re Marzocchi, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). See also MPEP §2164.04, rev. 2, May 2004, pg 2100-189.

The examiner must weigh all the evidence before him or her, including the specification and any new evidence supplied by applicant with the evidence and/or sound scientific reasoning previously presented in the rejection and decide whether the claimed invention is enabled. The examiner should never make the determination based on personal opinion. The determination should always be based on the weight of all the evidence. MPEP §2164.05, 8th edition, rev. 2, May 2004, pg 2100-190 to -191.

Applicants respectfully aver that the examiner has not met his or her initial burden to establish a reasonable basis to question the enablement provided for the claimed invention, and specifically address, below, how the art used to support the Office's enablement rejection is not sufficient to rebut the presumptively enabled specification.

Additionally, because the examiner must weigh all the evidence before him or her, the Office did not sufficiently consider and specifically address Dr. Short's previously submitted Rule 132 expert declaration regarding enablement, in which Dr. Short declared, inter alia, it would not have required any knowledge or guidance as to which are the specific structural elements, e.g., amino acid residues, that correlate with amidase activity to create variants of the exemplary nucleic acid and test them for the expression of polypeptides or peptides having amidase activity, with reasons to doubt the objective truth of the statements contained therein. Applicants respectfully aver that their arguments, and Dr. Short's expert declaration, are sufficient to rebut any possible *prima facie* case of lack of enablement, i.e., Applicants have presented persuasive arguments that one skilled in the art would be able to make and use the claimed invention using the application as a guide. The evidence provided by applicant need not be conclusive but merely convincing to one skilled in the art. MPEP 2164.05, 8th edition, rev. 2, May 2004, pg 2100-190 to -191.

The Patent Office cites art purportedly showing the "unpredictability of assigning function based on structural homology and how small changes can lead to major changes in function." Please see the Office action, e.g., page 9, lines 3 to 10, citing Bork (2000) Genome Res. 10:398-400; Broun et al. (1998) Science 282:1315-1317; Van de Loo et al. (1995) Proc. Natl. Acad. Sci. USA 92:6743-6747; Witkowski et al. (1999) Biochemistry 38:11643-11650; and Seffernick et al. (2001) J. of Bacteriol. 183:2405-2410. It is alleged that because such "critical structural element" knowledge was not taught, a large number of variants had to be created and tested - and the specification does not provide reasonable enablement for testing, or screening, this large number variants for amidase-encoding polynucleotides (the Office agreed that creation of the variants having the structural limitations recited in the claims is routine in the art, it is the testing aspect that concerns the Office).

However, none of these references, individually or in their totality, are sufficient to rebut the presumption of enablement. None of these references are directed

to whether, or not, screening (testing) a large number of nucleic acid variants (of an exemplary nucleic acid of the invention) for amidase-encoding activity would have constituted undue experimentation to one skilled in the art at the time of the invention.

Bork (2000) Genome Res. 10:398-400, discusses limits on computational sequence analysis. In Bork, there is no discussion regarding the merits or difficulties of protocols that screen for enzyme activity, e.g., screen for enzyme activity in a library of polypeptides expressed by a plurality of nucleic acid variants. Bork only questions the accuracy of assigning protein function only based on sequence identity. However, the amidase activity of polypeptides of the instant invention are not based only on sequence identity (homology) to known proteins, but rather are based on empirical, experimental data demonstrating that exemplary polypeptides of the invention have amidase activity (see, e.g., Examples 2 and 3, of the specification). Interestingly, Bork opines that most computational sequence analysis methodologies can predict function with an expected accuracy of about 70%.

Broun et al. (1998) Science 282:1315-1317, shows that a small number of amino acid reside changes in the catalytic site of a family of structurally related enzymes can result in a change in activity (in particular, Broun found that as few as four amino acid substitutions can convert an oleate 12-desaturase to a hydroxylase and as few as six result in conversion of a hydroxylase to a desaturase). However, in Broun, there is no discussion regarding the merits or difficulties of protocols that screen for enzyme activity, e.g., screen for enzyme activity in a library of polypeptides expressed by a plurality of nucleic acid variants. In fact, it appears that Broun considered screening for enzyme activity in their enzyme variants a routine process. There is no discussion on whether changes in non-catalytic site amino acid residues have any effect on enzyme activity. In fact, Broun's data suggest that most changes in an enzyme's amino acid sequence (e.g., non-catalytic site amino acid residues) are not important in determining, or changing, its catalytic specificity.

Van de Loo et al. (1995) Proc. Natl. Acad. Sci. USA 92:6743-6747, prepared a cDNA library from a castor-oil plant, obtained partial nucleotide sequences for 468 anonymous clones, identified several cDNA clones encoding a polypeptide of 387 amino acids with a predicted MW of 44,407 and with approximately 67% sequence homology to an oleate desaturase, and expressed a full-length clone in a transgenic tobacco, which resulted in the accumulation of low levels of 12-hydroxyoleic acid in seeds, indicating that the expressed clone encodes an oleate hydroxylase. Van de Loo opined that these results suggested that fatty acyl desaturases and hydroxylases share similar reaction mechanisms. However, in Van de Loo, there is no discussion regarding the merits or difficulties of protocols that screen for enzyme activity, e.g., screen for enzyme activity in a library of polypeptides expressed by a plurality of nucleic acid variants. In fact, it appears that Van de Loo considered screening for enzyme activity in their single expressed clone a routine process. Van de Loo also credited the high-throughput capabilities of automated DNA sequenators in the examination of their anonymous clones.

Witkowski et al. (1999) Biochemistry 38:11643-11650, also showed that a small number of amino acid reside changes in the catalytic site of a family of structurally related enzymes can result in a change in activity. Witkowski noted that beta-ketoacyl synthases involved in the biosynthesis of fatty acids and polyketides exhibit extensive sequence similarity and share a common reaction mechanism. Interestingly, Witkowski also noted that multiple sequence alignments identified catalytic sites and provided the first clues about the possible identities of residues that play critical roles in catalysis. In fact, as with Broun, Witkowski's data suggest that most changes in an enzyme's amino acid sequence (e.g., non-catalytic site amino acid residues) are not important in determining, or changing, its catalytic specificity. In Witkowski, there is no discussion regarding the merits or difficulties of protocols that screen for enzyme activity, e.g., screen for enzyme activity in a library of polypeptides expressed by a plurality of nucleic acid variants. It appears that Witkowski considered screening for enzyme activity a routine process.

Seffernick et al. (2001) J. of Bacteriol. 183:2405-2410, also shows that a small number of amino acid reside changes in the catalytic site of an enzyme can result in a change in activity. Seffernick compared a deaminase (melamine deaminase) with a hydrolase (atrazine chlorohydrolase, AtzA) and found that each enzyme consists of 475 amino acids and differs by only 9 amino acids. Seffernick opined that their data suggest that the 9 amino acid differences between melamine deaminase and AtzA represent a short evolutionary pathway connecting enzymes catalyzing physiologically relevant deamination and dehalogenation reactions. As with Broun and Witkowski, Seffernick's data suggest that most changes in an enzyme's amino acid sequence (e.g., non-catalytic site amino acid residues) are not important in determining, or changing, its catalytic specificity. In Seffernick, there is no discussion regarding the merits or difficulties of protocols that screen for enzyme activity, e.g., screen for enzyme activity in a library of polypeptides expressed by a plurality of nucleic acid variants. It appears that Seffernick also considered screening for enzyme activity a routine process.

Applicants respectfully aver that none of these references, individually or in their totality, are sufficient to rebut the instant application's presumption of enablement. None of these references are directed to whether, or not, screening a large number of nucleic acid variants would have constituted undue experimentation to one skilled in the art at the time of the invention. In fact, because Broun, Witkowski and Seffernick's data suggest that most changes in an enzyme's amino acid sequence (e.g., non-catalytic site amino acid residues) are not important in determining, or changing, its catalytic specificity, these references support the idea that most changes in an enzyme's amino acid sequence will result in little or no effect on its specificity or activity, and that one of skill in the art could easily target a minimum number of residues to generate a limited number of enzyme variants to generate desired enzyme variants.

As note above, while the Office agrees that creation of variants having the structural limitations recited in the claims is routine in the art, it is alleged, inter alia, that the specification does not provide reasonable enablement for testing, or screening, the

large number variants for amidase-encoding polynucleotides. The Patent Office alleged that it would have required some knowledge or guidance as to which are the specific structural elements, e.g., amino acid residues, that correlate with amidase activity to generate a reasonable number of variants and screen them, without undue experimentation, for amidase-encoding polynucleotides (please see page 9, lines 16 to 24, of the office action).

Applicants respectfully maintain that whether large numbers of compositions (e.g., variants of nucleic acids or proteins) must be screened to determine if one is within the scope of the claims is irrelevant to an enablement inquiry; please see Applicants response of February 12, 2004, e.g., pages 19 to 22. Enablement is not precluded by the necessity to screen large numbers of compositions, as long as that screening is "routine," i.e., not "undue," to use the words of the Federal Circuit. Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987). "Time and difficulty" are not determinative of undue experimentation if the experimentation is routine. See PPG Indus., Inc. v. Guardian Indus. Corp., 75 F.3d 1558, 1564, 37 USPQ2d 1618, 1623 (Fed. Cir. 1996). In Hybritech, Inc., the court was acknowledging that, because practitioners in that art are prepared to screen large numbers of negatives in order to find a sample that has the desired properties, the screening that would be necessary to make additional antibody species was not "undue experimentation." In Hybritech, Inc., the court acknowledged that, using 1980's technology, this was not "undue experimentation."

Analogously, practitioners in the art at the time of this invention were prepared to make and screen large numbers of negatives in order to find a sample with the desired properties, e.g., an amidase-encoding nucleic acid. Those skilled in the relevant art at the time of the instant claimed invention could, using the state of the art and Applicants' written disclosure, produce and screen a genus of nucleic acids (e.g., nucleic acids having 70%, 80%, 90% or 95% sequence identity to SEQ ID NO:1) for amidase-encoding activity without undue experimentation. Thus, the making and

screening that would be necessary to generate amidase-encoding nucleic acids, as set forth in the claimed methods, was not "undue experimentation."

Applicants' maintain that one skilled in the art at the time of the invention using the state of the art and the written disclosure could have screened a genus of nucleic acids for amidase-encoding activity without undue experimentation. The specification provided the skilled artisan a reasonable amount of guidance with respect to screening for amidases, i.e., screening variant nucleic acids to identify the claimed genus of amidase-encoding nucleic acids. For example, in Example 2, pages 84 and 85, and Example 3, pages 85 to 87, the specification provides exemplary protocols to identify and screen for amidases within the scope of the invention, and, amidase-encoding nucleic acids within the scope of the invention. Accordingly, the specification provides guidance on alternative, routine protocols for determining amidase activity that can be practiced without undue experimentation.

Furthermore, as declared by Dr. Short in the declaration submitted in Applicants' previous response (Dr. Short is an expert in the field of molecular biology and enzyme development and was an expert at the time of the invention, his resume as documentation of his credentials was submitted in Applicant's previous response), the state of the art at the time of the invention and the level of skill of the person of ordinary skill in the art, e.g., screening enzymes such as amidases, and nucleic acids encoding amidases, was very high. As declared by Dr. Short, using the teaching of the specification, one skilled in the art could have selected routine methods known in the art at the time of the invention to express variants of nucleic acids encoding the exemplary enzyme of the invention and screen them for expression of polypeptides having amidase activity. Dr. Short declared that one skilled in the art could have used routine protocols known in the art at the time of the invention, including those described in the instant specification, to screen for nucleic acids encoding polypeptides having a percent sequence identity to SEQ ID NO:1, or active fragments thereof, for amidase activity. Dr. Short declared that it was routine to screen for multiple substitutions or multiple

modifications of an enzyme-encoding (e.g., amidase-encoding) sequence and predictably achieve positive results. As declared by Dr. Short, while the numbers of samples needed to be screened may have been high, the screening procedures were routine and successful results (i.e., finding variant nucleic acids encoding amidases) predictable.

In the enclosed expert declaration, Dr. Short declares that it would not have been necessary for the skilled artisan to understand which specific regions or structural elements of an amidase were necessary for function or activity to routinely generate the genus of claimed amidase-encoding nucleic acids. Dr. Short declares that methods for making and screening enzymes were sufficiently comprehensive and routine at the time of the invention to predictably generate a genus of amidase-encoding sequences without need of knowing which specific regions or structural elements of a sequence or structure affected function or activity. Dr. Short declares that methods known at the time of the invention for modifying nucleic acid and polypeptide sequences in combination with known enzyme (amidase) screening protocols (e.g., high through-put screening) made methods that required previous knowledge of structural elements necessary for enzymatic activity obsolete and unnecessary. Dr. Short declares that enzyme screening methodologies, including high through-put screening, known at the time of the invention (including *in vivo* and *in vitro* nucleic acid expression and enzyme (amidase) screening protocols) made methods that require previous knowledge of protein structure, including secondary or tertiary structure, active site sequences, and the like obsolete and unnecessary. Dr. Short declares that by using methods known in the art at the time of the invention, including the amidase screening protocols described in the specification, it would not have been necessary to understand which specific regions of amidase structure needed to be modified to generate the claimed genus of nucleic acids without undue experimentation. Dr. Short declares that the specification provided sufficient guidance to one of ordinary skill in the art to make and use the genus of amidase-encoding nucleic acids to practice the methods of the invention. Accordingly, it would not have taken undue experimentation to make and use the claimed invention, including screening for and identifying the claimed genus of amidase-encoding nucleic acids.

As noted above, the Patent Office alleged that it would have required some knowledge or guidance as to which are the specific structural elements, e.g., amino acid residues, that correlate with amidase activity to generate a reasonable number of variants and screen them, without undue experimentation, for amidase-encoding polynucleotides. It was alleged that the specification is silent in regard to which are the amino acid residues with can be substituted, deleted or inserted into a nucleic acid to obtain structural, and functional, homologues.

However, Applicants respectfully note that the specification does provide guidance as to what amino acid substitutions can be made to make the genus of amidases of the invention. For example, paragraph 0048, on pages 11 to 12 of the specification, teaches

> ... a "substantially identical" amino acid sequence is a sequence that differs from a reference sequence by one or more conservative or non-conservative amino acid substitutions, deletions, or insertions, particularly when such a substitution occurs at a site that is not the active site of the molecule, and provided that the polypeptide essentially retains its functional properties. A conservative amino acid substitution, for example, substitutes one amino acid for another of the same class (*e.g.*, substitution of one hydrophobic amino acid, such as isoleucine, valine, leucine, or methionine, for another, or substitution of one polar amino acid for another, such as substitution of arginine for lysine, glutamic acid for aspartic acid or glutamine for asparagine). One or more amino acids can be deleted, for example, from an amidase polypeptide, resulting in modification of the structure of the polypeptide, without significantly altering its biological activity. For example, amino- or carboxyl-terminal amino acids that are not required for amidase biological activity can be removed. Modified polypeptide sequences of the invention can be assayed for amidase biological activity by any number of methods, including contacting the modified polypeptide sequence with an amidase substrate and determining whether the modified polypeptide decreases the amount of specific substrate in the assay or increases the bioproducts of the enzymatic reaction of a functional amidase polypeptide with the substrate.

Accordingly, the specification did provide guidance as to what amino acid changes could be made to make the genus of amidase-encoding nucleic acids used in the claimed methods.

Further addressing the Patent Office's concerns that because the claimed genera are very large sufficient guidance must be provided to determine which changes can be tolerated in a protein's amino acid sequence to obtain a desired activity to practice the invention without undue experimentation, Dr. Short declares that if the skilled artisan needed guidance as to which amino acid residues could be modified to obtain structural or functional variants of an enzyme of the invention (Applicants have maintained that it would not have been necessary for one skilled in the art to understand which specific regions of enzyme structure could be modified to generate the claimed genus of polypeptides without undue experimentation), that information was, inter alia, readily available in the form of amidase sequences known in the art at the time of the invention. Dr. Short declares that a routine, simple sequence alignment comparison of known amidase sequences would have identified regions of identity and dissimilarity to provide guidance to the skilled artisan as to which sequences could be changed, or not changed, to generate structural and/or functional variations of amidases or enzyme-encoding nucleic acids of the invention.

Furthermore, Dr. Short declares that direction to the skilled artisan as to which amino acid residues can be substituted, deleted or inserted into a nucleic acid to obtain structural, and functional, homologues of an amidase enzyme could also be found in the art at the time of the invention. For example, at the time of the invention one of skill in the art would have been aware of the many studies of amidase activity and active site structure, see, e.g., Chebrou (1996) Biochim. Biophys. Acta 1298(2):285-293, "Study of the amidase signature group"; Novo (1995) FEBS Lett. 367(3):275-279, "Pseudomonas aeruginosa aliphatic amidase is related to the nitrilase/cyanide hydratase enzyme family and Cys166 is predicted to be the active site nucleophile of the catalytic mechanism"; Tata (1994) Biochim Biophys Acta. 1205(1):139-145, "Arg-188 and Trp-144 are

implicated in the binding of urea and acetamide to the active site of the amidase from Pseudomonas aeruginosa". Accordingly, one skilled in the art at the time of the invention using the teaching of the specification had many sources of direction to determine which amino acid residues could be substituted, deleted or inserted into a nucleic acid to obtain structural, and functional, homologues of an amidase enzyme.

Accordingly, Applicants respectfully submit that the pending claims meet the written description and enablement requirements under 35 U.S.C. §112, first paragraph. In light of the above remarks, Applicants respectfully submit that amended claims are fully enabled by and described in the specification to overcome the rejection based upon 35 U.S.C. §112, first paragraph.

CONCLUSION

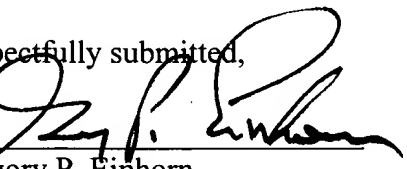
In view of the foregoing amendment and remarks, Applicants respectfully aver that the Examiner can properly withdraw the rejection of the pending claims under 35 U.S.C. §112, first and second paragraphs. Applicants respectfully submit that all claims pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

As noted above, Applicants have requested a telephone conference with the undersigned representative to expedite prosecution of this application. After the Examiner has reviewed the instant response and amendment, please telephone the undersigned at (858) 720-5133.

Applicants believe that no additional fees are necessitated by the present response and amendment. However, in the event any such fees are due, the Commissioner is hereby authorized to charge any such fees to Deposit Account No. 03-1952 referencing docket number 564462000420. Please credit any overpayment to this account.

Dated: January 25, 2005

Respectfully submitted,

By 

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